SEARCH REQUEST FORM (STIC)

Requestor's Name: David Lukton

Examiner number: 71263

8-15-05

Art Unit: 1654

Phone number: 571-272-0952

Serial Number:

10-719599

Mail Box: 3-C-70

Examiner Rm: 3-B-75

Results format: paper

Neuroprotective Agents Title:

Applicants: SUNDSTROM, LARS ERIC; IANNOTTI, FAUSTO; BRADLEY, MARK; PRINGLE, ASHLEY KER

Earliest Priority Date: 12/16/97

Applicants are claiming the compounds on the attached sheet.

 R^2 = hydrogen or alkyl or acyl or R-NHCO- (R = alkyl or aryl);

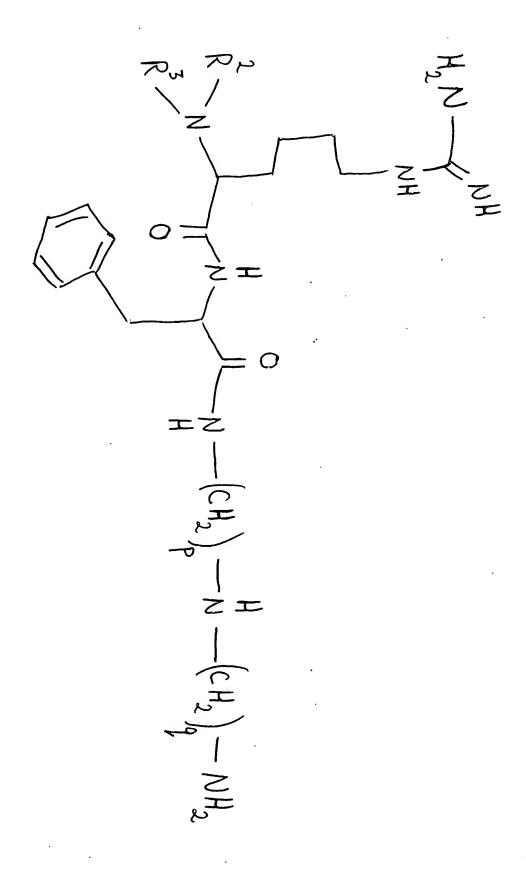
 R^3 = hydrogen or alkyl or acyl or R-NHCO-

(R = alkyl or aryl);

p = an integer of 3 or 4;

q = an integer of 3 or 4

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(FILE 'HOME' ENTERED AT 11:12:35 ON 12 MAY 2004)

FILE 'REGISTRY' ENTERED AT 11:12:46 ON 12 MAY 2004 STR

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L4 STR L1 L5 0 SEA SSS SAM L4 L6 1 SEA SSS FUL L4

1 SEA SSS FUL L4
17 1 SEA ABB=ON L3 OR L6 / compd. from Reg, - see done stot, affacked

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FILE 'CAOLD' ENTERED AT 11:23:33 ON 12 MAY 2004 0 SEA ABB=ON L7

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SELECT RN L8 1-2

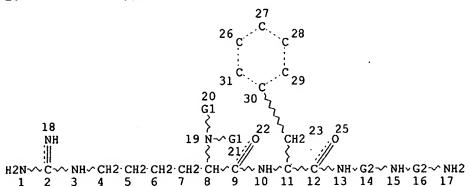
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L10

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FILE 'HCAPLUS' ENTERED AT 11:36:35 ON 12 MAY 2004
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=> d que stat 111 L4 STR



VAR G1=H/C/O REP G2=(3-4) CH2 NODE ATTRIBUTES: DEFAULT MLEVEL IS ATOM DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES: RING(S) ARE ISOLATED OR EMBEDDED NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE

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L7	1 SEA FILE=REGISTRY ABB=ON L5 OR L6
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	577692-72-9/BI)
L11	2 SEA FILE=HCAPLUS ABB=ON L8 AND L10

=> d ibib abs hitstr l11 1-2

L11 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2003:633453 HCAPLUS

DOCUMENT NUMBER:

139:159957

TITLE:

Spermidine derivatives for the treatment of chronic

neurodegenerative diseases

INVENTOR(S):

Morrison, Barclay, III; Pringle, Ashley Ker;

Sundstrom, Lars Eric; Wulfert, Ernst

PATENT ASSIGNEE(S):

University of Southampton, UK

SOURCE:

PCT Int. Appl., 52 pp.

Patent

CODEN: PIXXD2

DOCUMENT TYPE: LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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RN 19059-14-4 HCAPLUS

'CN Peroxynitrite (8CI, 9CI) (CA INDEX NAME)

O== N- O- O-

IT 577692-72-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(spermidine derivs. for treatment of chronic neurodegenerative diseases)

RN

577692-72-9 HCAPLUS
Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino)propyl]-5-CN (CA INDEX NAME) [(aminoiminomethyl)amino]-, (2S)-, trifluoroacetate (9CI)

CM

CRN 191277-14-2 CMF C13 H31 N7 O

Absolute stereochemistry.

$$H_2N$$
 (CH₂)₄ $(CH_2)_3$ N $(CH2)3 N $NH2$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

134951-15-8 191277-14-2 227758-28-3 IT 227758-30-7 227758-32-9 227758-33-0 227758-34-1 227758-35-2 227758-36-3 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (spermidine derivs. for treatment of chronic neurodegenerative RN 134951-15-8 HCAPLUS Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) CN (CA INDEX NAME)

Absolute stereochemistry.

191277-14-2 HCAPLUS RN

Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-CN [(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

RN 227758-28-3 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-30-7 HCAPLUS

CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-32-9 HCAPLUS

CN L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-[3-[(4-aminobutyl)amino)propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 NH
 $(CH_2)_4$
 S
 NH_2
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_4$

RN 227758-33-0 HCAPLUS

CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

RN 227758-34-1 HCAPLUS

CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino)propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-35-2 HCAPLUS

CN Glycinamide, L-arginyl-N-[3-((4-aminobutyl)amino)propyl]-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-36-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

$$H_2N$$
 $(CH_2)_4$
 N
 H
 $(CH_2)_3$
 N
 H
 NH_2
 NH_2

IT 222640-12-2 446882-39-9D, resin-bonded

RL: RCT (Reactant); RACT (Reactant or reagent)

(spermidine derivs. for treatment of chronic neurodegenerative

diseases)

222640-12-2 HCAPLUS RN

CN 2-0xa-4,9,11-triazadodecan-12-oic acid, 5-carboxy-11-[(1,1dimethylethoxy)carbonyl]-1-(9H-fluoren-9-yl)-10-imino-3-oxo-, 12-(1,1-dimethylethyl) ester, (5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 446882-39-9 HCAPLUS

1,3-Cyclohexanedione, 2-[1-[[3-[[4-[[(4-methoxyphenyl)diphenylmethyl]amino CN |butyl]amino]propyl]amino]ethylidene]-5,5-dimethyl- (9CI) (CA INDEX NAME)

REFERENCE COUNT:

5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

1999:404918 HCAPLUS

DOCUMENT NUMBER:

131:59135

TITLE:

Preparation of amino acid derivatives as

neuroprotective agents

INVENTOR(S):

Pringle, Ashley Ker; Bradley, Mark; Sundstrom, Lars Eric; Iannotti, Fausto

PATENT ASSIGNEE(S):

University of Southampton, UK

SOURCE:

PCT Int. Appl., 53 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.

KIND DATE

1

APPLICATION NO. DATE

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WO 9931049
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              MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
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         TJ, TM

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     NO 2000003075
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                        A1
                             20031003
                                                               20001215
PRIORITY APPLN. INFO.:
                                                           A 19971216
                                          GB 1997-26569
                                          WO 1998-GB3775
                                                            W 19981216
                                          WO 1999-GB1719
                                                            W 19990616
OTHER SOURCE(S):
                          MARPAT 131:59135
     Amino acid derivs. Q-Ra-C*H(NR2R3)CO-Zn-NR1-Rb-NH-Rc-NH-W [Q = amidino,
     cyano, or amino group; Ra, Rb, Rc = (un) substituted alkylene, alkenylene;
     R2, R3 = H, R, RCO, RO2C, RNHCO (R = (un) substituted alkyl or aryl); the
     chiral atom indicated by the asterisk is in the L configuration; Z is an
     amino acid residue; n = 0, 1; R1 = H, (un) substituted alkyl or aryl; W =
     H, alkyl, aryl] were prepared as neuroprotectants. Thus,
     N1-L-arginylspermidine, prepared by coupling of resin-bound spermidine
     derivative with protected arginine, followed by deprotection/cleavage using
     TFA-phenol-water-triisopropylsilane-1,2-ethanedithiol, showed 99.4 %
     protection (relative to control hypoxia in CA1 pyramidal cell layer).
     134951-15-8P 191277-14-2P 191277-15-3P
     227758-27-2P 227758-28-3P 227758-29-4P
     227758-31-8P 227758-32-9P 227758-33-0P
     227758-34-1P 227758-35-2P 227758-36-3P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of amino acid derivs. as neuroprotective agents)
RN
     134951-15-8 HCAPLUS
CN
     Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI)
     (CA INDEX NAME)
```

Absolute stereochemistry.

RN 191277-14-2 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_4$
 N
 H
 $(CH_2)_3$
 N
 H
 NH_2
 NH_2

RN 191277-15-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_4$
 $(CH_2)_3$
 $(CH_2)_3$
 $(CH_2)_3$
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_3$
 $(CH_2)_4$
 $(C$

RN 227758-27-2 HCAPLUS

CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_4$
 R
 N
 H
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 NH_2

RN 227758-28-3 .HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI)
 (CA INDEX NAME)

$$H_2N$$
 $(CH_2)_3$
 N
 H
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 NH_2

RN 227758-29-4 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-31-8 HCAPLUS

CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-,
 tetrakis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 227758-30-7 CMF C22 H40 N8 O2

Absolute stereochemistry.

$$H_{2N}$$
 NH
 NH
 $(CH_2)_3$
 S
 NH_2
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 227758-32-9 HCAPLUS

L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-[3-[(4aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME) Absolute stereochemistry.

$$H_2N$$
 NH
 $(CH_2)_4$
 S
 H
 $(CH_2)_4$
 NH_2
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$
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 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$

RN 227758-33-0 HCAPLUS

CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-34-1 HCAPLUS

CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-35-2 HCAPLUS

CN Glycinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-2-phenyl- (9CI) (CA INDEX NAME)

$$H_2N$$
 NH
 $(CH_2)_3$
 S
 NH_2
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$
 $(CH_2)_4$

RN 227758-36-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino)propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 227758-40-9 227758-41-0 227767-50-2

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of amino acid derivs. as neuroprotective agents)

RN 227758-40-9 HCAPLUS

CN Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-41-0 HCAPLUS

CN Pentanamide, 2-amino-N-[4-{(4-aminobutyl)amino]butyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227767-50-2 HCAPLUS

CN Pyridinepropanamide, α-amino-N-[3-[(4-aminobutyl)amino]propyl](9CI) (CA INDEX NAME)



 $\begin{array}{c|c} & \text{O} & \text{NH}_2 \\ & || & | \\ & \text{H}_2\text{N--} & (\text{CH}_2)_4 - \text{NH--} & (\text{CH}_2)_3 - \text{NH--} & \text{C--} & \text{CH}_2 - \text{D1} \\ \end{array}$

RN 110-60-1 HCAPLUS CN 1,4-Butanediamine (8CI, 9CI) (CA INDEX NAME)

 $H_2N-(CH_2)_4-NH_2$

RN 156-87-6 HCAPLUS CN 1-Propanol, 3-amino- (8CI, 9CI) (CA INDEX NAME)

H2N-CH2-CH2-CH2-OH

PAGE 1-A

PAGE 2-A

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Lukton 09/581,397

11/05/2004

=> d ibib abs ind hitstr 142 1-3

L42 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:753643 HCAPLUS

DOCUMENT NUMBER: 140:280736

TITLE: Characterisation of a novel class of polyamine-based

neuroprotective compounds

AUTHOR(S): Pringle, Ashley K.; Morrison, Barclay;

Bradley, Mark; Iannotti, Fausto;

Sundstrom, Lars E.

CORPORATE SOURCE: Clinical Neurosciences, University of Southampton,

Southampton, SO16 7PX, UK

SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2003),

368(3), 216-224

CODEN: NSAPCC; ISSN: 0028-1298

PUBLISHER:

Springer-Verlag

DOCUMENT TYPE: LANGUAGE:

Journal English

AB Prolonged cerebral ischemia initiates complex intra- and inter-cellular signalling cascades ultimately resulting in neuronal death.

Well-characterised mediators of ischemic cell death are glutamate, free radicals and nitric oxide. Many drugs that block these mechanisms are

neuroprotective in vitro, but have unfavorable side-effect profiles in man. We have recently demonstrated that the compound L-arginyl-3,4-spermidine (L-Arg3,4) is neuroprotective in vitro through an interaction with several of these mechanisms, and prevents ischemic neurodegeneration in vivo with no gross side effects. In this study, we have used solid-phase combinatorial chemical, to synthesize a number of analogs of L-Arg3,4, and investigate the structure-activity relationship using an in vitro, organotypic hippocampal slice culture model of cerebral ischemia. A number of mol. features were identified which were essential for the neuroprotective activity including the requirement for a pos. charge and an amino acid in the L-configuration. Relatively minor alterations to both the terminal arginine and polyamine moieties significantly attenuated neuroprotective efficacy. Our data implies that these compds. are neuroprotective through a currently undefined mechanism rather than non-specific ionic interactions described previously for other

polyamine-containing compds.
CC 1-3 (Pharmacology)

ST structure activity neuroprotectant polyamine ischemia brain hippocampus

IT Brain

(hippocampus; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)

IT Brain, disease

(ischemia; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)

IT Cytoprotective agents

(neuroprotective; structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)

IT Structure-activity relationship

(structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs)

IT c 134950-93-9 134951-15-8 141997-14-0

191277-14-2 227758-27-2 227758-28-3

227758-29-4 227758-36-3 227758-40-9

227758-41-0 675606-34-5 675606-35-6

675606-36-7 675606-37-8 675606-38-9

675606-39-0 675606-40-3

RL: PAC (Pharmacological activity); BIOL (Biological study) (structure and neuroprotective activity of polyamine-based

L-arginyl-3, 4-spermidine analogs) 134950-93-9 134951-15-8 141997-14-0 IT 191277-14-2 227758-27-2 227758-28-3 227758-29-4 227758-36-3 227758-40-9 227758-41-0 675606-34-5 675606-35-6 675606-36-7 675606-37-8 675606-38-9 675606-39-0 675606-40-3 RL: PAC (Pharmacological activity); BIOL (Biological study) (structure and neuroprotective activity of polyamine-based L-arginyl-3,4-spermidine analogs) 134950-93-9 HCAPLUS RN Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-[4-[(3-CN aminopropyl)amino]butyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 N
 H
 $(CH_2)_4$
 N
 NH_2
 NH_2

134951-15-8 HCAPLUS RN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) CN (CA INDEX NAME)

Absolute stereochemistry.

141997-14-0 HCAPLUS RN

Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-[3-[(3-CN aminopropyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$\begin{array}{c|c} & \text{NH} & \text{O} & \text{CH}_2)_3 \\ & \text{NH}_2 & \text{NH}_2 & \text{NH}_2 \\ \end{array}$$

RN

191277-14-2 HCAPLUS
Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-CN [(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

RN 227758-27-2 HCAPLUS

CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino)propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-28-3 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-{(4-aminobutyl)amino}propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_3$
 N
 H
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 NH_2

RN 227758-29-4 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_3$
 R
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 NH_2

RN 227758-36-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

227758-40-9 HCAPLUS RN

Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) CN (CA INDEX NAME)

Absolute stereochemistry.

227758-41-0 HCAPLUS RN

Pentanamide, 2-amino-N-[4-[(4-aminobutyl)amino]butyl]-5-CN [(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

675606-34-5 HCAPLUS RN

1H-Imidazole-4-propanamide, α -amino-N-[3-[(4-CN aminobutyl)amino]propyl]-, (aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN

675606-35-6 HCAPLUS Hexanamide, 2,6-diamino-N-[4-[(4-aminobutyl)amino]butyl]-, (2S)- (9CI) CN (CA INDEX NAME)

RN 675606-36-7 HCAPLUS

CN Pentanamide, 2-amino-5-[(aminoiminomethyl)amino]-N-(8-aminooctyl)-, (2S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 675606-37-8 HCAPLUS

CN Pentanamide, N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-2-[(phenylmethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 675606-38-9 HCAPLUS

CN Carbamic acid, [(1S)-1-[[[3-[(4-aminobutyl)amino]propyl]amino]carbonyl]-4[(aminoiminomethyl)amino]butyl]-, phenylmethyl ester (9CI) (CA INDEX

Absolute stereochemistry.

RN 675606-39-0 HCAPLUS

CN Pentanamide, N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]2-[(phenylsulfonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 675606-40-3 HCAPLUS

CN Pentanamide, 2-(acetylamino)-N-[3-[(4-aminobutyl)amino)propyl]-5[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:4310 HCAPLUS

DOCUMENT NUMBER: 139:30604

TITLE: L-Arginyl-3, 4-spermidine is neuroprotective in several.

in vitro models of neurodegeneration and in vivo

ischaemia without suppressing synaptic transmission

AUTHOR(S): Morrison, Barclay, III; Pringle, Ashley K.;

McManus, Terence; Ellard, John; Bradley, Mark

; Signorelli, Francesco; Iannotti, Fausto;

Sundstrom, Lars E.

CORPORATE SOURCE: Division of Clinical Neurosciences, School of

Medicine, Bassett Crescent East, University of

Southampton, Southampton, SO16 7PX, UK

SOURCE: British Journal of Pharmacology (2002), 137(8),

1255-1268

CODEN: BJPCBM; ISSN: 0007-1188

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal LANGUAGE: English

AB 1 Stroke is the third most common cause of death in the world, and there is a clear need to develop new therapeutics for the stroke victim. To address this need, we generated a combinatorial library of polyamine compds. based on sFTX-3.3 toxin from which L-Arginyl-3,4-spermidine (L-Arg-3,4) emerged as a lead neuroprotective compound In the present study, we have extended earlier results to examine the compound's neuroprotective actions in greater detail. 2 In an in vitro ischemia model, L-Arg-3,4 significantly reduced CA1 cell death when administered prior to induction of 60 min of ischemia as well as when administered immediately after ischemia. Surprisingly, L-Arg-3,4 continued to prevent cell death significantly when administration was delayed for as long as 60

min after ischemia. 3 L-Arg-3,4 significantly reduced cell death in excitotoxicity models mediated by glutamate, NMDA, AMPA, or kainate. Unlike glutamate receptor antagonists, 300 µM L-Arg-3,4 did not suppress synaptic transmission as measured by evoked responses in acute hippocampal slices. 4 L-Arg-3,4 provided significant protection, in vitro, in a superoxide mediated injury model and prevented an increase of superoxide production after AMPA or NMDA stimulation. It also decreased nitric oxide production after in vitro ischemia and NMDA stimulation, but did so without inhibiting nitric oxide synthase directly. 5 Furthermore, L-Arg-3,4 was significantly neuroprotective in an in vivo model of global forebrain ischemia, without any apparent neurol. side-effects. 6 Taken together, these results demonstrate that L-Arg-3,4 is protective in several models of neurodegeneration and may have potential as a new therapeutic compound for the treatment of stroke, trauma, and other neurodegenerative diseases.

- CC 1-11 (Pharmacology)
- ST arginylspermidine neuroprotective forebrain ischemia stroke
- IT Glutamate receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AMPA-binding; arginylspermidine is neuroprotective in several in vitro
models of neurodegeneration and in vivo ischemia without suppressing
synaptic transmission)

IT Brain, disease

(forebrain, ischemia; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Brain

(hippocampus, sector CA1, cell death inhibition; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Cytoprotective agents

(neuroprotective; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Toxicity

(neurotoxicity, excitotoxicity; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Brain, disease

(stroke; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Neurotransmission

(synaptic; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT Nerve

(toxicity, excitotoxicity; arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT 56-86-0, L-Glutamic acid, biological studies 487-79-6,

Kainic acid 6384-92-5 10102-43-9, Nitric oxide,

biological studies 11062-77-4, Superoxide

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT 191277-14-2

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

IT 56-86-0, L-Glutamic acid, biological studies 487-79-6, Kainic acid 6384-92-5 10102-43-9, Nitric oxide,

biological studies 11062-77-4, Superoxide

RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

RN 56-86-0 HCAPLUS

CN L-Glutamic acid (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 487-79-6 HCAPLUS

CN 3-Pyrrolidineacetic acid, 2-carboxy-4-(1-methylethenyl)-, (2S,3S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

RN 6384-92-5 HCAPLUS

CN D-Aspartic acid, N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 10102-43-9 HCAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

n== 0

RN 11062-77-4 HCAPLUS

CN Superoxide (8CI, 9CI) (CA INDEX NAME)

o = 0

IT 191277-14-2

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(arginylspermidine is neuroprotective in several in vitro models of neurodegeneration and in vivo ischemia without suppressing synaptic transmission)

RN

191277-14-2 HCAPLUS
Pentanamide, 2-amino-N-[3-{(4-aminobutyl)amino]propyl}-5-CN [(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_4$
 N
 H
 $(CH_2)_3$
 N
 H
 NH_2
 NH_2

REFERENCE COUNT:

THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS 45 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L42 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

1999:404918 HCAPLUS

DOCUMENT NUMBER:

131:59135

TITLE:

Preparation of amino acid derivatives as

neuroprotective agents

INVENTOR (S):

Pringle, Ashley Ker; Bradley, Mark ; Sundstrom, Lars Eric; Iannotti,

Fausto

PATENT ASSIGNEE(S):

SOURCE:

University of Southampton, UK

PCT Int. Appl., 53 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	TENT	NO.		KIND DATE APPLICATION NO. DATE													
WO	9931	931049 F				1999	0624		WO 1998-GB3775 1998121								
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ΑU	9915	717		Α	1	1999	0705		A	U 19	99-1	5717		1998	1216		
ΑU	7392	96		В:	2	2001	1011										
EP	1040	096		A	1	2000	1004		Ε	P 19	98-9	6003	1	1998	1216		
EP	1040	096		В	1	2003	0709										

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     JP 2002508349
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                       A3
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                       A3
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         R: AT, BE,
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                                            нк 2000-108125
                             20031003
     HK 1029331
                       A1
                                                             19971216
                                         GB 1997-26569
                                                          А
PRIORITY APPLN. INFO .:
                                         WO 1998-GB3775
                                                          W
                                                              19981216
                                         WO 1999-GB1719
                                                           W
                                                              19990616
OTHER SOURCE(S):
                         MARPAT 131:59135
     Amino acid derivs. Q-Ra-C*H(NR2R3)CO-Zn-NR1-Rb-NH-Rc-NH-W [Q = amidino,
     cyano, or amino group; Ra, Rb, Rc = (un) substituted alkylene, alkenylene;
     R2, R3 = H, R, RCO, RO2C, RNHCO (R = (un) substituted alkyl or aryl); the
     chiral atom indicated by the asterisk is in the L configuration; Z is an
     amino acid residue; n = 0, 1; R1 = H, (un) substituted alkyl or aryl; W =
     H, alkyl, aryl] were prepared as neuroprotectants. Thus,
     N1-L-arginylspermidine, prepared by coupling of resin-bound spermidine
     derivative with protected arginine, followed by deprotection/cleavage using
     TFA-phenol-water-triisopropylsilane-1,2-ethanedithiol, showed 99.4 %
     protection (relative to control hypoxia in CAl pyramidal cell layer).
     ICM C07C237-10
IC
     ICS C07C257-14; A61K031-155; A61K031-16
     34-2 (Amino Acids, Peptides, and Proteins)
CC
     arginylspermidine prepn neuroprotectant; spermidine arginyl prepn
     neuroprotectant
     Structure-activity relationship
IT
        (neuroprotectant; preparation of amino acid derivs. as neuroprotective
        agents)
ΙT
     Cytoprotective agents
        (neuroprotectants; preparation of amino acid derivs. as neuroprotective
        agents).
ΙT
     Ischemia
        (preparation of amino acid derivs. as neuroprotective agents)
IT
     Amino acids, preparation
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of amino acid derivs. as neuroprotective agents)
     134951-15-8P 191277-14-2P 191277-15-3P
ΙT
     227758-27-2P 227758-28-3P 227758-29-4P
     227758-31-8P 227758-32-9P 227758-33-0P 227758-34-1P 227758-35-2P 227758-36-3P
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (preparation of amino acid derivs. as neuroprotective agents)
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227758-40-9 227758-41-0 227767-50-2

IT

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of amino acid derivs. as neuroprotective agents)

IT 110-60-1, 1,4-Butanediamine 156-87-6

227758-37-4D, resin-bound

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of amino acid derivs. as neuroprotective agents)

IT 227758-39-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of amino acid derivs. as neuroprotective agents)

IT 134951-15-8P 191277-14-2P 191277-15-3P

227758-27-2P 227758-28-3P 227758-29-4P

227758-31-8P 227758-32-9P 227758-33-0P

227758-34-1P 227758-35-2P 227758-36-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of amino acid derivs. as neuroprotective agents)

RN 134951-15-8 HCAPLUS

CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 191277-14-2 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 191277-15-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminoiminomethyl)amino]-, (2R)- (9CI) (CA INDEX NAME)

RN 227758-27-2 HCAPLUS

CN Hexanamide, 2,6-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI)

(CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 $(CH_2)_4$
 R
 $(CH_2)_3$
 N
 H
 $(CH_2)_4$
 NH_2

RN 227758-28-3 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino)propyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-29-4 HCAPLUS

CN Pentanamide, 2,5-diamino-N-[3-[(4-aminobutyl)amino]propyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$(CH_2)_3$$
 $(CH_2)_3$ $(CH_2)_4$ $(CH_2)_4$

RN 227758-31-8 HCAPLUS

CN L-Phenylalaninamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-, tetrakis(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 227758-30-7 CMF C22 H40 N8 O2 Absolute stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 227758-32-9 HCAPLUS

CN L-Phenylalaninamide, N6-(aminoiminomethyl)-L-lysyl-N-(3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_{2N}$$
 NH
 $(CH_2)_4$
 S
 NH_2
 $(CH_2)_3$
 $(CH_2)_4$
 $(CH_2)_4$

RN 227758-33-0 HCAPLUS

CN L-Tyrosinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-34-1 HCAPLUS

CN L-Tryptophanamide, L-arginyl-N-[3-[(4-aminobutyl)amino)propyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-35-2 HCAPLUS

CN Glycinamide, L-arginyl-N-[3-[(4-aminobutyl)amino]propyl]-2-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 227758-36-3 HCAPLUS

CN Pentanamide, 2-amino-N-[3-[(4-aminobutyl)amino]propyl]-5-[(aminocarbonyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 227758-40-9 227758-41-0 227767-50-2

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of amino acid derivs. as neuroprotective agents)

RN 227758-40-9 HCAPLUS

CN Pentanediamide, 2-amino-N1-[3-[(4-aminobutyl)amino]propyl]-, (2S)- (9CI) (CA INDEX NAME)

RN 227758-41-0 HCAPLUS

CN Pentanamide, 2-amino-N-[4-[(4-aminobutyl)amino]butyl]-5-[(aminoiminomethyl)amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

$$H_2N$$
 (CH₂) 4 N_H (CH₂) 4 N_H S (CH₂) 3 N_H NH₂

RN 227767-50-2 HCAPLUS

CN Pyridinepropanamide, α-amino-N-[3-[(4-aminobutyl)amino]propyl](9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & \text{O} & \text{NH}_2 \\ & \parallel & \parallel & \parallel \\ \text{H}_2\text{N--} & \text{(CH}_2)_4 - \text{NH-----} & \text{(CH}_2)_3 - \text{NH-----} & \text{C------} & \text{CH}_2 - \text{D1} \end{array}$$

IT 110-60-1, 1,4-Butanediamine 156-87-6

227758-37-4D, resin-bound

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of amino acid derivs. as neuroprotective agents)

RN 110-60-1 HCAPLUS

CN 1,4-Butanediamine (8CI, 9CI) (CA INDEX NAME)

 $H_2N-(CH_2)_4-NH_2$

RN 156-87-6 HCAPLUS

CN 1-Propanol, 3-amino- (8CI, 9CI) (CA INDEX NAME)

H2N-CH2-CH2-CH2-OH

RN 227758-37-4 HCAPLUS

CN 13-0xa-2,6,11-triazapentadecanoic acid, 6-[2-amino-1-[4-[(benzoyloxy)carbonyl]phenoxy]-2-oxoethyl]-14,14-dimethyl-12-oxo-,

9H-fluoren-9-ylmethyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

IT 227758-39-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of amino acid derivs. as neuroprotective agents)

RN 227758-39-6 HCAPLUS

CN 1,3-Cyclohexanedione, 2-[1-[(3-hydroxypropyl)amino]ethylidene]-5,5dimethyl- (9CI) (CA INDEX NAME)

2

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Page 17